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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 07/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/608,783	NIGAM ET AL.	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-67* is/are pending in the application.

4a) Of the above claim(s) *8-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 10 April 2006 to claims 1-3 and 7 have been entered. Claims 1-67 remain pending in the current application, with claims 8-67 being withdrawn from consideration. Claims 1-7 have been considered on the merits.

Priority

Applicant's claim for the benefit under 35 U.S.C. 119(e) to provisional application 60/426,152 (filed 14 November 2002) is acknowledged. Applicant's claim for benefit under 35 U.S.C. 119 to international application PCT/US02/20673 (filed 28 June 2002), which further claims priority to US provisional application 60/301,684 (filed 28 June 2001), is acknowledged. All claims are appropriately noted in the first paragraph of the specification.

However, the declaration submitted by applicant further notes claims for priority under 35 U.S.C. 120 to applications 09/595,195 and 09/965,651; such claims for priority are not noted in the first paragraph of the specification, as is required by 37 CFR1.78. Furthermore, applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 to 09-595,195 and/or 09/965,651 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior applications. The disclosure of the invention in the parent applications and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 09/956,651 & 09/595,195, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112

for claims 3-7 of this application. While applicant has incorporated the teachings of 09/956,651 and 09/595,195 into the current application it is required that the parent applications contain the subject matter claimed in the current application, not vice versa. Neither of the prior-filed applications discloses the propagation of ureteric bud tissue in culture in the presence of pleiotrophin and/or heregulin or active fragments thereof. Therefore, the subject matter of claims 3-7 is not fully supported by the prior filed applications.

Claim Objections

Claim 1 remains objected to: URETERIC is still spelled incorrectly in the first line of the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-7 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, applicants' claim 3 recites pleiotrophin and/or heregulin or an active fragment thereof, claim 4 recites GDNF or a functional equivalent thereof, and claim 5 recites FGF1 or a functional equivalent thereof.

"An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention... one must define a compound by 'whatever characteristics sufficiently distinguish it'. A lack of adequate written description issue also arises if the

knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process." MPEP § 2163

Regarding the active fragments of pleiotrophin and/or heregulin, there is no evidence that the inventors were in possession of isolated active fragments of pleiotrophin and/or heregulin at the time of filing. To satisfy the written description aspect of 35 U.S.C. 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. The specification does not disclose any representative species of active fragments of heregulin or pleiotrophin that have the ability to induce branching morphogenesis of ureteric bud tissue, with or without identifying characteristics, such as chemical structure, nucleic acid or protein sequence information. Therefore, claims 3-7 fail to satisfy the written description requirement.

Regarding the functional equivalents of GDNF and FGF1, there is insufficient written description provided in the disclosure to adequately describe the precise action GDNF and/or FGF1 have on the branching morphogenesis of ureteric bud cells; therefore, without description of the function of GDNF and/or FGF1 in this particular method, one of ordinary skill in the art would not be able to immediately envisage all the functional equivalents thereof. Furthermore, there is no evidence that the inventors were in possession of functional equivalents of homologues of GDNF and/or FGF1 at the time of filing, particularly in light of the fact applicant has failed to disclose the relevant, identifying characteristics, such as structure, physical and/or chemical characteristics, and structure and that they have failed to present a representative number of species which could be used as 'functional equivalents' of GDNF and/or FGF1 in the present method. *See Eli Lilly,* 119F. 3d. at 1568, 43 USPQ2d at 1406.

Claims 1-7 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing ureteric bud cells to undergo branching morphogenesis in culture comprising culturing ureteric bud cells in either BSN-CM and/or pleiotrophin, does not reasonably provide enablement for inducing UB cells to undergo branching morphogenesis in culture comprising only heregulin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Applicant's claims are directed to methods of culturing UB cells so as to induce branching morphogenesis, claims 1 and 2 are silent on the culture conditions, claims 3-7 particularly require culture in culture medium comprising pleiotrophin and/or heregulin. The alternative language used in claim 3 allows for the use of culture medium comprising only one of pleiotrophin and heregulin. At the time of the invention, it was known that UB cells cultured in the presence of BSN conditioned media (derived from metanephric mesenchymal cells) would surprisingly undergo branching morphogenesis; addition of glial derived neurotrophic factor (GDNF) would increase the rate and degree of branching morphogenesis (See, e.g. Qiao et al, PNAS 1999). However, it was not clear what specific morphogenic factors, present in the BSN-CM, were responsible for the branching morphogenesis. In the present application applicants have set forth evidence that they have discovered the 18 kDa protein pleiotrophin is at least one of the main morphogenic factors responsible for the branching morphogenesis of the UB cells in 3-D culture (See Spec, particularly Pg. 37). Applicants provide surprising evidence that pleiotrophin, a heparin-binding factor, is capable of inducing impressive branching morphogenesis of isolated UB cells; however, while applicants hypothesize that additional morphogenic growth-promoting factors are present in the BSN-CM, they fail to provide similarly compelling evidence that any other factors, namely heregulin, have similar morphogenic growth-promoting ability on the UB cells.

In the present specification, filed 27 June 2003, applicants state they have identified heregulin in BSN-CM (See Spec. Pg. 42, paragraph 00140); they further state, "it is very likely that heregulin is one of the factors that induce UB growth." However, such a statement is not supported by evidence, as applicants have only shown that UBs grown in the presence of isolated heregulin plus GDNF and FGF1 grew to a "similar" morphology as UBs grown in the presence of non-pleiotrophin-containing fractions of BSN-CM (See Spec, pg 42, paragraph 00140). No description of the morphology is provided for cultures grown in the non-pleiotrophin-containing fractions; therefore there is no evidence that either of the UB populations described above underwent any degree of branching morphogenesis; in fact, because pleiotrophin was shown to be a critical morphogenic growth-promoting factor, and pleiotrophin was not present in either of the culture mediums, one would expect that neither of the populations of UBs (cultured in presence of heregulin alone, or cultured in presence of pleiotrophin-free fractions) would have undergone branching morphogenesis. Doubt is further cast on the ability of heregulin to, by itself, induce branching morphogenesis based on the complete lack of mention in any of the post-published non-patent literature, including applicants' own paper ("Identification of pleiotrophin as a mesenchymal factor involved in ureteric bud branching morphogenesis" Development, 2001) or reviews of molecular controls in branching morphogenesis (Piscione et al, Differentiation, 2002).

While lack of any working examples cannot be the sole factor in determining enablement, the lack of evidence of the ability of heregulin to induce branching morphogenesis, the lack of teachings or guidance provided in the specification regarding the ability of heregulin to induce branching morphogenesis, the unpredictability of the art- as evidenced by the lack of identification of any morphogenic growth-promoting factors in BSN-CM prior to applicants' identification of pleiotrophin, and the lack of recognition in the art, even post-filing, of heregulin or other factors present in BSN-CM capable of inducing branching morphogenesis, as a whole support that applicants were not enabled for the claimed invention as a whole, but were rather limited to use of pleiotrophin.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants' claim 1 is directed to a method of propagating ureteric bud cells in culture, comprising (a) culturing a UB in vitro under conditions that induce the UB to undergo branching morphogenesis to generate a population of UBs comprising tubular branches; (b) subdividing the UB population; and (c) resuspending each subpopulation in culture media and repeating (a) and (b). Claim 2 requires the conditions to comprise culturing the UB in the presence of BSN-CM, FGF1, and GDNF.

Regarding claim 1, it remains unclear what 'conditions' induce the UB to under go branching morphogenesis. Though claim 2 defines the conditions as culturing in the presence of BSN-CM, FGF1, and GDNF, each claim must stand on its own; therefore, claim 1 fails to particularly point out and distinctly claim the subject matter which applicant regards as their invention. The use of BSN-CM appears to be critical to the invention, as the specification submits "Conditioned medium secreted by metanephric mesenchyme-derived cells [BSN-CM] is required for isolated UB branching morphogenesis.... Thus, BSN-CM contains and additional soluble factor(s) necessary for epithelial cell branching morphogenesis." (Spec, Pg. 33, paragraphs 00115-00116).

Applicants' claim 3 is directed to a method for the in vitro culture and propagation of ureteric bud tissue, comprising isolating ureteric bud tissue from mesenchymal tissue obtained from embryonic kidney rudiments; culturing the isolated ureteric bud tissue in a biocompatible matrix in the presence of a culture medium comprising pleiotrophin and/or heregulin or an active fragment thereof for a sufficient time and

under sufficient conditions to produce tubular branches within the biocompatible matrix; separating the plurality of branched tips to generate bud fragments; and culturing each bud fragment in a biocompatible matrix with a culture medium comprising pleiotrophin and/or heregulin or an active fragment thereof. Claim 4 requires the culture medium to further comprise a GDNF or a functional equivalent thereof. Claim 5 requires the culture medium to further comprise FGF1 or a functional equivalent thereof. Claim 6 requires the biocompatible matrix to comprise cotton, collagen, polyglycolic acid, cat gut suture, cellulose, gelatin, dextran, polyamide, polyester, polystyrene, polypropylene, polyacrylate, polyvinyl, polycarbonate, polytetrafluorethylene, nitrocellulose compound, or Matrigel. Claim 7 requires the gelatin to be treated to contain proteoglycans, Type I collagen, Type IV collagen, laminin, fibronectin, or combinations thereof.

Regarding claim 3, the step of culturing the isolated ureteric bud tissue under sufficient conditions so as to produce tubular branches is unclear. It is not clear what is considered 'sufficient conditions' to induce branching morphogenesis; as these parameters appear to be critical to inducing branching morphogenesis, it is necessary to fully disclose these particular conditions within the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 6 and 7 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sakurai et al (PNAS, 1997), in view of "Basic Techniques for Mammalian Cell Tissue Culture" (Current Protocols in Cell Biology, 1998), Naughton et al (US 2003/0007954), and "Overview of Extracellular Matrix" (Current Protocols in Cell Biology, 1998).

Applicants' claim 1 is directed to a method of propagating ureteric bud cells in culture, comprising (a) culturing a UB in vitro under conditions that induce the UB to undergo branching morphogenesis to generate a population of UBs comprising tubular branches; (b) subdividing the UB population; and (c) resuspending each subpopulation in culture media and repeating (a) and (b).

Applicants' claim 3 is directed to a method for the in vitro culture and propagation of ureteric bud tissue, comprising isolating ureteric bud tissue from mesenchymal tissue obtained from embryonic kidney rudiments; culturing the isolated ureteric bud tissue in a biocompatible matrix in the presence of a culture medium comprising pleiotrophin and/or heregulin or an active fragment thereof for a sufficient time and under sufficient conditions to produce tubular branches within the biocompatible matrix; separating the plurality of branched tips to generate bud fragments; and culturing each bud fragment in a biocompatible matrix with a culture medium comprising pleiotrophin and/or heregulin or an active fragment thereof. Claim 6 requires the biocompatible matrix to comprise cotton, collagen, polyglycolic acid, cat gut suture, cellulose, gelatin, dextran, polyamide, polyester, polystyrene, polypropylene, polyacrylate, polyvinyl, polycarbonate, polytetrafluorethylene, nitrocellulose compound, or Matrigel. Claim 7 requires the gelatin to be treated to contain proteoglycans, Type I collagen, Type IV collagen, laminin, fibronectin, or combinations thereof.

Sakurai et al teach a method of propagating ureteric bud cells in culture, comprising isolating ureteric bud tissue from embryonic kidney mesenchyme, suspending ureteric bud (UB) cells in an extracellular matrix gel (a biocompatible matrix), and culturing the UB cells in the presence of BSN-CM, derived from BSN cells of the metanephric mesenchyme, or in serum free media supplemented with several growth factors. For culture with the BSN-CM Sakurai et al used two different ECM gels, one comprising 80% type I collagen and 20% Matrigel, and one consisting of only type I collagen (Claims 6 and 7). For culture with the growth factors the ECM gel consisted of type I collagen. Sakurai et al noted that within 24-48 hours UB cells cultured in the presence of HGF, EGF, TGF-alpha, bFGF, IGF1 and

BSN-CM demonstrated tubulogeneic activity (See Sakurai et al, Pg. 6282, col. 2 & Fig. 5); therefore both the BSN-CM and the noted growth factors are considered conditions that induce the UB to undergo branching morphogenesis to generate a population of UBs comprising tubular branches (Claim 1). BSN-CM inherently comprises pleiotrophin and heregulin, as evidenced by the present application; though Sakurai et al did not specifically identify the presence of pleiotrophin and/or heregulin in the BSN-CM, it was still present in the culture medium (Claims 3, 6 and 7).

While Sakurai et al do not specifically teach subdividing the cultured UB cells/branch tips (to generate what applicant calls bud fragments) and resuspending each subpopulation in culture medium and repeating the culture step, it would have been well within the purview of one of ordinary skill in the art, as part of routine animal cell tissue culture methods, to divide and resuspend subpopulations of the UB cells (Claims 1 and 3). One of ordinary skill in animal cell tissue culture recognizes the need to routinely subculture cells by dividing and replating/resuspending the animal cells in order to propagate growth and maintain viability of animal cell and/or tissue culture (See Current Protocols in Cell Biology, 1.1.1). Therefore, in order to maintain a viable cell tissue culture the skilled artisan would have been motivated to continually subculture the growing UB cells and would have expected success in doing so because mammalian cell tissue culture techniques are well known in the art.

Regarding the biocompatible matrix material, Sakurai et al teach use of a Matrigel ECM gel supplemented with type I collagen(See Sakurai et al, Pg. 6281, col. 2), as well as pure collagen ECM gels (See Sakurai et al, Pg. 6282, col. 2); however, it would have been well within the purview of one of ordinary skill in the art at the time the invention was made to use a biocompatible matrix comprising any suitable tissue scaffold material treated with any natural extracellular matrix proteins. Suitable biocompatible matrix materials are well known in the art (See Naughton et al); generally materials for three-dimensional tissue culture should allow cells to attach, or be treated so that cells may attach, and allow cells to grow in more than one layer (See Naughton et al, Pg. 2, paragraph 0031). Naughton et al

teach suitable biocompatible matrix materials include nylon (polyamides), Dacron (polyesters), polystyrenes, polypropylenes, polyacrylates, polyvinyls, polycarbonates, polytetrafluorethylene, polyglycolic acid, nitrocelluloses, cotton, cat gut sutures, celluloses, gelatin, collagen and dextran (See Naughton et al, Pg. 2, paragraphs 0032-0033). Naughton et al further teach the biocompatible materials can be further treated with extracellular matrix proteins to enhance adhesion, including collagen, elastin, glycoproteins (See Naughton et al, page 3, paragraph 0040). Additional ECM proteins known in the art to be useful for enhancing adhesion of cells to substrates include fibril forming collagens (including type I collagen), network forming collagens (including type IV collagen), fibronectin, laminin, and proteoglycans (See "Overview of Extracellular Matrix"). Therefore, at the time the invention was made it would have been obvious to one of ordinary skill in the art to alternatively use any known, suitable biocompatible matrix material, such as those taught by Naughton et al, and to treat the matrix material with any of the known cell adhesion-enhancing proteins, such as those described in "Overview of Extracellular Matrix" (Claims 6 and 7). The functional equivalency of the matrix materials is recognized in the prior art; therefore it would have been *prima facie* obvious to substitute any of the known matrix materials for the Matrigel or collagen materials utilized by Sakurai et al for the same purpose of culturing the UB cells. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1, 3, 4, 6 and 7 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Qiao et al (PNAS, 1999), i n view of "Basic Techniques for Mammalian Cell Tissue Culture" (Current Protocols in Cell Biology, 1998), Naughton et al (US 2003/0007954), and "Overview of Extracellular Matrix" (Current Protocols in Cell Biology, 1998).

Applicants' claim 1 is directed to a method of propagating ureteric bud cells in culture, comprising (a) culturing a UB in vitro under conditions that induce the UB to undergo branching

morphogenesis to generate a population of UBs comprising tubular branches; (b) subdividing the UB population; and (c) resuspending each subpopulation in culture media and repeating (a) and (b).

Applicants' claim 3 is directed to a method for the in vitro culture and propagation of ureteric bud tissue, comprising isolating ureteric bud tissue from mesenchymal tissue obtained from embryonic kidney rudiments; culturing the isolated ureteric bud tissue in a biocompatible matrix in the presence of a culture medium comprising pleiotrophin and/or heregulin or an active fragment thereof for a sufficient time and under sufficient conditions to produce tubular branches within the biocompatible matrix; separating the plurality of branched tips to generate bud fragments; and culturing each bud fragment in a biocompatible matrix with a culture medium comprising pleiotrophin and/or heregulin or an active fragment thereof. Claim 4 requires the culture medium to further comprise GDNF. Claim 6 requires the biocompatible matrix to comprise cotton, collagen, polyglycolic acid, cat gut suture, cellulose, gelatin, dextran, polyamide, polyester, polystyrene, polypropylene, polyacrylate, polyvinyl, polycarbonate, polytetrafluorethylene, nitrocellulose compound, or Matrigel. Claim 7 requires the gelatin to be treated to contain proteoglycans, Type I collagen, Type IV collagen, laminin, fibronectin, or combinations thereof.

Qiao et al teach isolating ureteric bud tissue from embryonic kidney rudiments of rats and suspending the isolated UB in an extracellular matrix gel (biocompatible matrix) consisting of type I collagen and Matrigel (See Qiao et al, Pg. 7330, col. 1); the UB cells were cultured in the presence of BSN culture media (BSN-CM) and a growth factor mixture containing EGF, HGF, IGF, FGF2, and GDNF for a sufficient time and under sufficient conditions to undergo branching morphogenesis (See Qiao et al, Pg. 7332, col. 1 & Fig. 2-3). BSN-CM inherently comprises pleiotrophin and heregulin, as evidenced by the present application; though Qiao et al did not specifically identify the presence of pleiotrophin and/or heregulin in the BSN-CM, it was still present in the culture medium (Claims 1, 3, 4, 6 and 7).

While Qiao et al do not specifically teach subdividing the cultured UB cells/branch tips (to generate what applicant calls bud fragments) and resuspending each subpopulation in culture medium and repeating the culture step, it would have been well within the purview of one of ordinary skill in the art, as part of routine animal cell tissue culture methods, to divide and resuspend subpopulations of the UB cells (Claims 1 and 3). One of ordinary skill in animal cell tissue culture recognizes the need to routinely subculture cells by dividing and replating/resuspending the animal cells in order to propagate growth and maintain viability of animal cell and/or tissue culture (See Current Protocols in Cell Biology, 1.1.1). Therefore, in order to maintain a viable cell tissue culture the skilled artisan would have been motivated to continually subculture the growing UB cells and would have expected success in doing so because mammalian cell tissue culture techniques are well known in the art.

Regarding the biocompatible matrix material, Qiao et al teach use of a Matrigel ECM gel supplemented with type I collagen (See Qiao et al, Pg. 7330, col. 1); however, it would have been well within the purview of one of ordinary skill in the art at the time the invention was made to use a biocompatible matrix comprising any suitable tissue scaffold material treated with any natural extracellular matrix proteins. Suitable biocompatible matrix materials are well known in the art (See Naughton et al); generally materials for three-dimensional tissue culture should allow cells to attach, or be treated so that cells may attach, and allow cells to grow in more than one layer (See Naughton et al, Pg. 2, paragraph 0031). Naughton et al teach suitable biocompatible matrix materials include nylon (polyamides), Dacron (polyesters), polystyrenes, polypropylenes, polyacrylates, polyvinyls, polycarbonates, polytetrafluorethylene, polyglycolic acid, nitrocelluloses, cotton, cat gut sutures, celluloses, gelatin, collagen and dextran (See Naughton et al, Pg. 2, paragraphs 0032-0033). Naughton et al further teach the biocompatible materials can be further treated with extracellular matrix proteins to enhance adhesion, including collagen, elastin, glycoproteins (See Naughton et al, page 3, paragraph 0040). Additional ECM proteins known in the art to be useful for enhancing adhesion of cells to

substrates include fibril forming collagens (including type I collagen), network forming collagens (including type IV collagen), fibronectin, laminin, and proteoglycans (See "Overview of Extracellular Matrix"). Therefore, at the time the invention was made it would have been obvious to one of ordinary skill in the art to alternatively use any known, suitable biocompatible matrix material, such as those taught by Naughton et al, and to treat the matrix material with any of the known cell adhesion-enhancing proteins, such as those described in "Overview of Extracellular Matrix" (Claims 6 and 7). The functional equivalency of the matrix materials is recognized in the prior art; therefore it would have been *prima facie* obvious to substitute any of the known matrix materials for the Matrigel/collagen material utilized by Qiao et al for the same purpose of culturing the UB cells. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments received 10 April 2006 have been considered. Each argument is addressed below, as appropriate. Objections/Rejections not repeated above have been withdrawn due to the amendments to the claims.

In response to the rejection of claims 3-7 under 35 USC 112, first paragraph, as lacking written description for active fragments of pleiotrophin and heregulin and functional equivalents of FGF1 and GDNF, applicants argue that pleiotrophin, GDNF and FGF1 are all well known in the art, and their sequences known. Applicant provides the GenBank accession number for pleiotrophin; applicants argue that because pleiotrophin was known, it would not have been undue experimentation for one of ordinary skill in the art to assay pleiotrophin. Regarding GDNF and FGF1, applicants argue that because of the lengths of these peptides, it would not require undue experimentation for the skilled artisan to obtain functional equivalents or homologues thereof. Applicants do not comment on active fragments of heregulin.

Applicants' arguments are not found persuasive. It is acknowledged that the whole proteins were known in the art at the time the invention was made; however, the rejection was based on the fact that the application does not provide evidence that applicants had possession of **active fragments** of heregulin and pleiotrophin or **functional equivalents** of FGF1 or GDNF. Applicants assertion that it would not be undue experimentation for one of ordinary skill in the art to assay pleiotrophin to determine the active fragments, or do identify functional equivalents of FGF1 and GDNF does not serve to obviate the rejection based on lack of written description, as undue experimentation is a factor in considering enablement, not in determining whether written description is provided for. Furthermore, it has been held that merely a wish or plan for obtaining the chemical invention claimed (such as by screening a library or assaying a compound) does not provide adequate written description of chemical invention, rather a precise definition, such as by structure, formula, chemical name, or physical properties, is required. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004). In order to satisfy the written description requirement for a genus of molecules, such as **active fragments** of heregulin and pleiotrophin and **functional equivalents** of FGF1 and GDNF, identifying characteristics of the claimed molecules must be disclosed in the form of structure, physical and/or chemical characteristics, or functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these, and a representative number of species within the genus must be disclosed. Applicants have not identified any particular structural, physical or chemical characteristic of any of the molecules in question, nor have they provided a single example of an active fragment of heregulin or pleiotrophin, or a single example of a functional equivalent of FGF1 or GDNF.

In response to the rejection of claim 1-7 under 35 USC, 112, first paragraph for lacking enablement for use of heregulin alone to induce ureteric bud cells to undergo branching morphogenesis,

applicants argue that the specification teaches that heregulin may be used along with or as a substitute for pleiotrophin (specifically pointing to Pages 13-14 of the specification). Applicants further argue that one skilled in the art can readily anticipate the use of heregulin to provide similar morphogenic growth-promoting ability on the UB cells (presumably the same as pleiotrophin).

Applicants arguments are found unpersuasive. The arguments presented are considered to be the arguments of counsel, are unsupported by evidence or declarations of those skilled in the art, and is thus of no probative value to support the case of enablement of the claimed invention. It is recognized that the specification does state that heregulin can be used in addition to or as an alternative to pleiotrophin; however, for the reasons set forth in the rejection above, the use of heregulin alone is not considered enabled. Regarding applicants statement that one skilled in the art can readily anticipate the use of heregulin to provide morphogenic growth-promoting ability on the UB cells is likewise unsubstantiated. Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See MPEP § 2129 and § 2144.03 for a discussion of admissions as prior art.

In response to the rejection of claims 1-7 under 35 USC 112, second paragraph, indefiniteness, applicants argue that, based on the disclosure, independent claims 1 and 3 are clear with respect to specific conditions and amounts of time necessary to successfully carry out the claimed methods. Applicants cite *In re Halleck* to support the stance that the phrase "an effective amount...for growth stimulation" has been held to be definite when the amount was not critical and those skilled in the art would be able to determine from the written disclosure what an effective amount is. Applicants do not provide any support for their position that 'sufficient conditions' is clear.

These arguments are found persuasive in part. Applicants' argument regarding the term 'effective amount' (with regards to the duration of the culture periods) is found persuasive; one of

ordinary skill in the art would be able to determine, based on the disclosure and routine optimization practice, appropriate time periods for culture. However, while the length (time) of the cultures would be routinely optimized, because the length of time is not critical to the culture, but can be optimized and altered based on variables within the culture, the culture conditions, including the specific media components, are considered critical to the instant invention, and thus the phrase 'effective conditions' is not sufficient to particularly point out and define the invention. The identification of pleiotrophin as the active agent in BSN culture medium is the crux of the current invention, yet claim 1 omits this element completely. The instant specification does not unequivocally define 'culture conditions necessary for propagation of ureteric bud cells' throughout the specification several different culture conditions are provided for, resulting in varying degrees of success. The decision in *In re Halleck* is not binding with respect to the culture conditions, as this is not considered a result effective variable.

In response to the rejection under 35 USC 103(a) over Sakurai et al, in view of Current Protocol is Cell Biology and Naughton et al. Applicants argue that the examiner has used improper hindsight reconstruction to arrive at the instant invention, specifically to arrive at the conclusion that it would have been obvious to one of ordinary skill in the art to divide and resuspend a cell culture in order to maintain its viability. Applicants further argue that neither Current Protocols nor Naughton et al teach or suggest the biocompatible matrix of the invention, nor do they add anything to the teachings of Sakurai et al. Finally applicants argue that one of ordinary skill in the art would not have been motivated to use GDNF in the culture of the ureteric buds, as Sakurai et al teach GDNF is a poor morphogenic factor.

Applicants' arguments are not found persuasive. First, regarding applicants assertion that the examiner relied on impermissible hindsight reconstruction to show that it would have been well within the purview of one of ordinary skill in the art to subdivide and resuspend a cell/tissue culture, note that any judgment on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but

so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the invention was made, such is proper. See *In re McLaughlin* 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971). Routine division and subculture of cell and tissue cultures is routine in the art (See Current Protocols in Cell Biology), the idea to subdivide a growing cell culture most certainly was not solely derived from the instant application, but has been known and practiced since the beginning of cell cultures. Second, regarding applicants argument that neither Current Protocols nor Naughton et al teach the biocompatible matrices claimed: "Naughton et al teach suitable biocompatible matrix materials include nylon (polyamides), Dacron (polyesters), polystyrenes, polypropylenes, polyacrylates, polyvinyls, polycarbonates, polytetrafluorethylene, polyglycolic acid, nitrocelluloses, cotton, cat gut sutures, celluloses, gelatin, collagen and dextran (See Naughton et al, Pg. 2, paragraphs 0032-0033). Naughton et al further teach the biocompatible materials can be further treated with extracellular matrix proteins to enhance adhesion, including collagen, elastin, glycoproteins (See Naughton et al, page 3, paragraph 0040). Additional ECM proteins known in the art to be useful for enhancing adhesion of cells to substrates include fibril forming collagens (including type I collagen), network forming collagens (including type IV collagen), fibronectin, laminin, and proteoglycans (See "Overview of Extracellular Matrix")." Third, regarding applicants argument that Sakurai et al provides no motivation to include GDNF, but in fact teaches away from the use of GDNF, it is noted that none of the claims rejected over Sakurai et al include limitations directed to GDNF; Sakurai et al was not relied upon to show that inclusion of GDNF would have been obvious.

Applicants provide no arguments or traverse to the rejection of claims 1-7 under 35 USC 103(a) over Qiao et al, in view of Current Protocols in Cell Biology and Naughton et al. Therefore the rejection of record stands.

In response to the provisional obvious-type double patenting rejection, applicants have filed a terminal disclaimer over application 09-595,195. The obvious-type double patenting rejection is withdrawn.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Allison M Ford
Examiner
Art Unit 1651

LEON B. LANKFORD, JR.
PRIMARY EXAMINER